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Registered Randomized Trials Comparing Generic and Brand-Name Drugs: A Survey

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Abstract

Objectives: To evaluate the research agenda of registered randomized trials comparing generic and brand-name drugs in terms of who sponsors them, whether they are published promptly, and whether they find favorable results.

Methods: We included randomized trials comparing the safety or efficacy of brand-name vs generic medications that were registered in ClinicalTrials.gov or other registries from January 1, 2000, through July 31, 2015. To identify published articles or results generated from such trials, we searched PubMed, Scopus, Google, and registry databases. Data were compared across sponsorship categories ("inbred" if the compared drugs were owned by the same company or its partners/subsidiaries, "competitive" if the compared drugs were owned by competing companies, and "apparently nonprofit"), and time to publication was evaluated with Cox analysis.

Results: We found 207 registered protocols reporting on 186 completed trials. Among those trials, 37 had published their results and another 56 had posted results in registries, for a total of 93 trials with available results. Four years after trial completion, results were available for 64 of 138 trials (46.4%), with substantial differences by sponsor: 70.8% (34 of 48), 28.1% (18 of 64), and 46.2% (12 of 26) of the inbred, competitive, and nonprofit trials, respectively. In multivariate modeling, inbred trials had a 1.73-fold risk of having results available compared with competitive trials (P=.04). Almost all trials reported favorable results, with the exception of 4 (4.3% of the 93 trials with results).

Conclusion: Despite the importance of generic drugs, relatively few registered randomized trials have compared the health effects of generic vs brand-name medicines, and there is an associated unsatisfactory publication rate and almost ubiquitous favorable results. The overall literature on the topic is at high risk of bias, possibly in favor of generic drugs. Higher nonprofit funding and stronger pressure to register trials and publish results are needed.

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Generic drugs are generally cheaper than their brand-name counterparts,[1] and there is increasing interest in using them more extensively. High-quality recommendations, based on the best available evidence and prompting the wider use of generic drugs, are thus strongly needed. However, the crucial assumption of identical health benefits of generic and brand-name drugs is still based on only a few systematic reviews of studies comparing cardiovascular[2-5] and antiepileptic[6,7] drugs. It would be interesting to appraise how extensive the corpus of registered randomized trials is for comparisons of generic vs brand-name counterparts. Important questions can be asked: Who is running these trials? Are their results published promptly? What do their results suggest? Is there evidence of bias in their dissemination?

As for other research fields,[8-10] in the case of studies comparing generic vs brand-name drugs there are ethical, legal, and scientific reasons to support the accurate, unbiased, and timely dissemination and publication of trial results.[11,12] A growing body of evidence indicates that a relevant proportion of results from randomized clinical trials (RCTs) remains unpublished or is published after major

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delay.[8-10,12-19] In these surveys, incomplete or selective reporting was documented in trials from different medical fields,[9,10,13,16] both industry-sponsored and non—industry-sponsored.[17] Moreover, there is some evidence that trials of head-to-head comparisons often tend to favor the sponsor.[20] To our knowledge, however, no study has been specifically designed to evaluate registration and publication patterns of trials comparing a generic vs a brand-name drug, their sponsorship background, and whether they publish results that are mostly favorable for the sponsors. To address these issues, we carried out a survey of registered RCTs comparing generic vs brand-name medicines.

METHODS

Search of Trial Registries and Data Extraction

We initially searched for RCTs that directly compared at least one brand-name drug and at least one of its generic versions, reported at least one efficacy or safety outcome, and had been registered in one or more of several clinical trial registries (US ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, International Standard Randomized Controlled Trial Number Registry, and Indian, Australian-New Zealand, and Chinese clinical trial registries) from January 1, 2000, through July 31, 2015. Two investigators (M.E.F., L.M.) independently performed the search using the following terms: *generic* OR *brand-name* OR *branded* OR *test formulation* OR *reference formulation*. No language restrictions were used. The searches were performed between February 1 and May 31, 2015.

Within the registries, we excluded trials terminated or withdrawn before the start of the study, nonrandomized trials, trials focusing on and reporting only bioequivalence measures (eg, drug serum concentration, time until maximum concentration, area under the curve based on serum concentration as a function of time), and duplicate registry entries. To grant a reasonable time for publishing, we considered only the trials that started before December 31, 2013,[13] and follow-up for the publication of the results was censored on August 1, 2015.

Eligible studies were scrutinized to extract the following data: trial registration code; starting date; completion status and completion date; type of drug(s) under comparison and corresponding Anatomical Therapeutic Chemical class; study location(s); sample size (as listed in the section "planned or actual enrollment" in the enrollment field); study design (noninferiority/equivalence or superiority); type of outcome (safety and/or efficacy); and type of funding source (brand-name manufacturers, generic manufacturers, and nonprofit institutions, as defined subsequently). In case of trials with "unknown" completion status (n=8), we classified them as completed if more than 2 years had passed from the estimated primary completion date. For the 6 trials that were reported as completed but the date of completion was missing, we extracted the expected duration of the study (or the expected duration of follow-up). Two trials did not report a start date; in these cases, we used the date of first enrollment if available and if that date was missing, the date of inclusion in the registry.

Type of Funding Source

We classified trials according to whether they had any funding from drug companies. Among trials that had funding from one or more companies, we further classified them according to whether they compared drugs that were all owned by the same company and its partners/subsidiaries ("inbred" trials) or whether they compared drugs that were owned/manufactured by different companies with no visible financial relationship between generic and brand-name drug manufacturers/owners ("competitive trials").

A trial was classified as funded by a drug company (either a generic or a brand-name drug manufacturer) if an explicit acknowledgment of support from private industry was declared in the corresponding trial registration record or in the published article. In case of multiple sources of funding, a trial was considered industry funded if at least one of the sponsors was a drug manufacturer, regardless of the presence of other nonprofit sources of funding.[20] It is possible, however, that some RCTs failed to disclose all the funding sources and personal financial ties of the principal investigators, given that some academic researchers

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